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Review Article

Medicine for novel therapy

The Effect of Cardiac Surgery in Children with Trisomy 13 And Trisomy 18: A Systematic Review and Meta-Analysis

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Abstract: Infants with trisomy 13 or trisomy 18 frequently suffer from cardiac anomalies. Our study aims to look at the impact of using cardiac surgery on mortality and functional outcome in patients with trisomy 13 and trisomy 18. A search for articles was done on PubMed, Scopus, Science Direct and CENTRAL databases; from inception until 30th October 2022. Quantitative analysis was done using Meta XL and Review Manager 5.4. A p=-value of 0.05 was adopted as the significance threshold. The database search yielded 1,127 articles but only 17 were included in this systematic review. This paper reports a total of 2,551 trisomy cases. 672 cases were T13, 1478 cases were T18 and 401 cases were undefined. The calculated Odds Ratio (OR) was 4.20 95%CI, 2.70 - 6.52], with a p-value < 0.00001. There was also the finding that cardiac surgery had a more positive impact on mortality and discharge outcomes for T18 patients than T13 patients. The difference, however was statistically insignificant. In conclusion, the use of cardiac surgery to manage T13 and T18 patients is plausible, but other factors like post-operative complications should be taken into account.

Keywords: Cardiac Surgery; Trisomy 13; Trisomy 18; Systematic Review; Meta-Analysis

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1. INTRODUCTION

Trisomy 13, also known as Patau syndrome, is a chromosomal abnormality where some or all of an individual's body cells contain extra genetic material from chromosome 13; making it three copies instead of the usual two [1] Trisomy 13, also known as Patau syndrome, is a chromosomal abnormality where some or all of an individual's body cells contain extra genetic material from chromosome 13; making it three copies instead of the usual two [1]. Full trisomy 13 is caused by chromosomal nondisjunction during meiosis and mosaic trisomy 13 is caused by nondisjunction during mitosis [1,2]. The presence of extra genetic material disrupts the normal course of development leading to multiple and complex organ defects [2]. This causes problems such as significant intellectual disability and physical abnormalities in the offspring. Individuals with trisomy 13 mostly suffer heart defects, brain or spinal cord degeneration and diseases, very small or undeveloped eyes (microphthalmia), extra fingers or toes, a cleft lip with or without an opening in the roof of the mouth (a cleft palate), and inadequate muscle tone (hypotonia) [2-4]. Thomas Bartholin became the first person to observe Trisomy 13-like symptoms in 1657 [5]. Still, the chromosomal nature of the ailment was ascertained in 1960 by Dr Eeva Therman and Dr Klaus Patau, whom the disease is named after [6]. Trisomy 18 also known as Edwards syndrome or Trisomy E is also a genetic anomaly arising from the presence of a third copy of chromosome 18, either in whole or in part [7,8]. The diagnostic conditions that define trisomy 18 seem to be the same as those for trisomy 13 [9,10]. The disease was first identified by John Hilton Edwards in 1960[11], though he attributed the aetiology to chromosome 17. Research work done by Klaus Patau and Eeva Therman would go on to identify the extra presence of chromosome 18 as the underlying etiology [12,13]. Trisomy 13 is the third most common trisomy after trisomy 21(Down syndrome) and T18. In 2017, Noriega & Siddik, [14], reported an occurrence rate of 1 in 10,000 to 20,000 live births. As of 2022, the Support Organization for Trisomy puts cases at 1 in 10,000-25,000 live-born infants, with an estimated 80% being full T13 [15]. 95% of T13 cases die during the antenatal period[16]. Of the affected infants who survive pregnancy and birth, only 6 to 12%, survive beyond the first year of life [17]. In the case of trisomy 18, as reported by the Support Organization for Trisomy, the current incidence rates are at 1 in 7,000 live-born infants, with over 90% of the cases being full T18[18]. Of these cases, Zoler, [19] estimates that only 8 to 12% of them survive past one year. These reports [17-19] are mildly supported by a retrospective study of 254 Canadian children done by Nelson et al., [20]. Nelson et al., [20] reports a one-year survival rate of 12.6% (95% CI, 8.9%-17.1%) and a ten-year survival rate of 9.8% (95% CI, 6.4%-14.0%) for trisomy 18. Although the mortality rate is high, there is no specific treatment for T13 or T18 [21]. The management procedure varies from case to case, largely depending on the severity of symptoms. From a literature review, treatment focuses on specific physical problems like neurological damage and complex heart defects [21-23]. Physical, occupational, and speech therapy also help to improve the developmental growth of those affected [23]. The most common intervention is surgical; this is done to manage physical problems arising from the diagnosis of T13 or T18. Nelson et al., [20] investigated the impact of available surgical interventions on survival in children with trisomy 13 and 18. They discovered that children who underwent surgery had a greater one-year survival rate than children who did not. The rates were 70.7% (95% CI, 54.3%-82.2%) for T13 and 68.6% (95% CI, 50.5%-81.2%) for T18. Muneuchi et al. [24] narrowed down the scope of treatment and looked at the effectiveness of cardiac surgery using a study population of 9 patients. The group that received cardiac surgery showed a survival rate of 25% and 22 % at 1 and 2 years, compared to 9% and 9% in the non-surgery group [24].

1.1. Justification for research

From the preliminary research conducted for this review, several articles reported on and supported the use of surgical intervention for T13 and T18 patients. One such article is Pallotto & Lantos, [21]. From reviewing 2 research articles, Pallotto & Lantos, [21], in their literature review, agreed on the beneficial possibility of using cardiac surgery to manage symptoms arising from T13 and T18. However, to the best of this paper's research, a systematic review on this topic has yet to be published.

1.2. Study Objective and Research Question.

This paper aims to fill the aforementioned gap by performing a systematic review guided by the research question: What is the effectiveness of using cardiac surgery in the management of trisomy 13 and trisomy 18? This question is formulated following the PICO guidelines.
Population – Infants diagnosed with trisomy 13 or trisomy 18.
Intervention – Cardiac surgery (all types)
Control – Non-cardiac surgery, any other intervention when possible.
Outcomes– Survival rate, quality of life.

1.3. Search Methodology

This systematic review was carried out following guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [25].

1.4. Information Sources

A systematic search for articles was done on PubMed, Scopus, ScienceDirect and the Cochrane Central Register of Controlled Trials (CENTRAL) databases; from inception until 30th October 2022. The search was done using a search string developed from topic keywords. The word string was first developed for use in PubMed and adopted for use in other databases. The search strings used are detailed in the Table below.

Table 1: Search strings

Database	Search field	Search String
PubMed/ Science Direct	Title, Abstract, Keywords	("cardiac surgery" OR "congenital heart surgery" OR "heart surgery") AND ("trisomy 13" OR T13OR "trisomy 18" OR T18)
Scopus	All fields	ALL (("cardiac surgery" OR "congenital heart surgery" OR "heart surgery") AND ("trisomy 13" OR t13 OR "trisomy 18" OR t18))
Central	All fields	("cardiac surgery" OR "congenital heart surgery" OR "heart surgery") AND ("trisomy 13" OR T13 OR "trisomy 18" OR T18)

No date range was used in any of the index databases.

1.5. Inclusion and exclusion criteria

The eligibility criteria that were developed expanded the PICO-formatted research question. The article had to be written in the English language and published before 30th October 2022. The study population had to be infants who were clinically diagnosed with either T13 or T18. Only original (primary data) articles were considered eligible. The treatment had to be a form of cardiac surgery explicitly, delivered alone or in combination, to a portion of or the entire study population. The existence of two groups (intervention and comparison) wasn't of much concern. The primary outcome was mortality/ survival rate. For articles to be excluded, they had to be of a secondary study design i.e, systematic reviews, letters to editors, paper comments, meta-analyses, and research articles. Also, articles that did not report on the effect of cardiac surgery in the management of T13 and T18 were excluded on the grounds of topic irrelevancy.

2. REVIEW METHODOLOGY

2.1. Study Selection process

Articles identified from the study search were subjected to a selection process as defined by the PRISMA guidelines. The process was carried out using resources made available by the Zotero software application.

2.2. Study Quality Assessment

The methodological quality of the included studies was assessed using the Newcastle-Ottawa scale for cohort studies. The maximum possible score was 8.

2.3. Data Extraction

Data from the included studies were extracted into two tables. The first table contained the author's/authors' name/names, study design, population size, type of trisomy, age at surgery, size of the surgery group, the size of the comparator group, cardiac anomalies in the study population, and the type of cardiac surgery administered. The second table contained the in-hospital mortality rate, overall mortality and the discharge rate for both the surgical and the comparator groups when possible. In-hospital mortality was defined as the number of deaths between admission and discharge. The overall mortality was defined as the total number of fatalities presented in the study.

2.4. Statistical Analysis

Quantitative analysis was done using Meta XL and Review Manager 5.4. Meta XL was used to calculate the prevalence/percent occurrence of events in the surgical groups and the non-surgical groups. Review Manager 5.4 was used to calculate the measure of association (odds ratio) between the intervention (cardiac surgery) and the outcomes (mostly, mortality rates). A p-value of 0.05 was adopted as the significance threshold.

3. RESULTS

3.1. Search Results

The initial search identified 1,127 articles. 113 duplicates were removed. During title and abstract screening, 945 articles were excluded following the eligibility criteria, and the remaining 69 articles were subjected to full-text review. In addition, 52 articles were excluded because they did not fully satisfy the eligibility criteria. Some articles were excluded for more than one reason. The reasons for exclusion are shown in the PRISMA flowchart below. At the end of the process, only 17 articles were included in this review paper. The study selection process is shown in Figure 1 below.

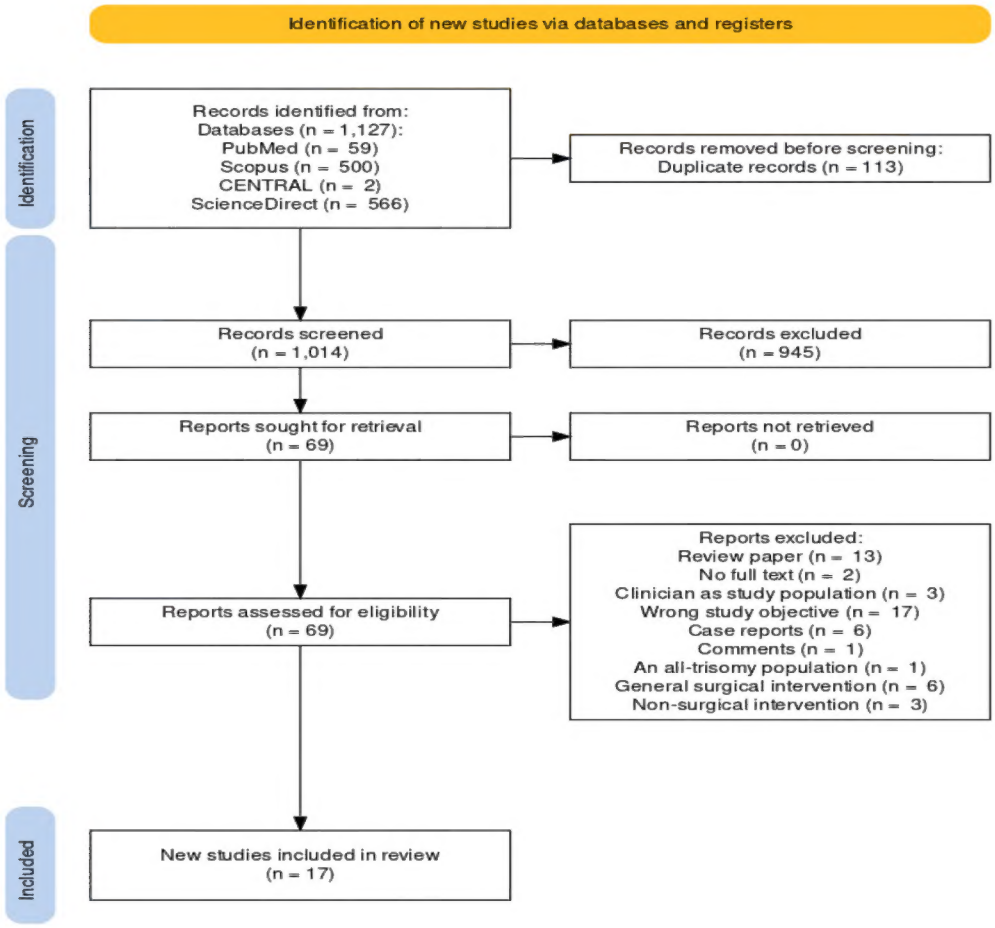

Fig 1: PRISMA flowchart showing the study selection process

3.2. *Quality Appraisal*

All 17 studies were found to be of high quality, with scores of 6 (28) (30) (31) (34) (38) (39) (40), 7 (27) (36) (41), and 8 (24) (26) (29) (32) (33) (35) (37). The results of the quality assessment are shown in Table 4.

3.3. *Data Extraction Results*

Table 2: Study Descriptor Table

Study	Study design	N	Trisomy	mean age at surgery	Surgery Group	Comparator group	Cardiac anomalies	type of surgery
Muneuchi et al., [24]	RCS	34	T18	37 weeks	9	25	VSD (2), PDA (1), VSD with ASD and/or PDA (5), DORV with/without MS (1)	PAB (4), ICR (3), Ligation (1), PBA + SFA (1)
Costello et al., [26]	RCS	13	T18	105 ± 94 days	7	6	VSD + PDA (3), VSD+PDA+ASD (2), TOF + PA (1), DORV with unbalanced AC, hypoplastic left ventricle + PDA (1)	VSD closure + PDA ligation (3), VSD/ASD closure, PDA ligation (2), PDA ligation (2)
		3	T13	NR	1	2	TOF (1)	Tetralogy of Fallot repair (1)
Bruns & Martinez, [27]	Cohort study	84	T18	range, 2 weeks to 41 months	24	NC	VSD (8), PDA (5), VSD + ASD (5), VSD + PDA (13), VSD+ ASD +PDA (25)	VSD repair (15), PDA repair (10), ASD repair (10), TOF repair (3)
Kwak et al., [28]	RCS	11	T18	827.5 days	11	0	VSD (8), PA+VSD (1), CoA/IAA+VSD(1), HLHS+IAA+VSD(1)	PDA ligation+ PA banding(7), PA banding (1), VSD closure + ASD closure (5), VSD closure + ASD closure + PDA ligation (1)

Rosenblum et al., [29]	RCS	45	T18	550.27 days	11	34	VDA (10), tetralogy of Fallot (7), Arch hypoplasia (1), PDA (1)	VSD repair (42.1%) TOF repair (36.8%) PDA closure, surgical 1 (5.3%) Sinus venosus ASD, VSD, valvuloplasty, aortic (5.3%) COA repair (5.3%) PA banding (5.3%)
		19	T13	252 days	8	11		
Cooper et al., [30]	RCS	270 op	T18	3.7 months (1.5–9.4)	270 op	0	VSD (146), TOF (16), PDA (20), VSD+CoA/aortic arch hypoplasia (15), ASD (9), COA (8), Single ventricle (7), AVSD, complete (5), TOF with pulmonary atresia (3), UK (41)	VSD repair (90), PAB (50), PV/RVOT reconstruction (26), TOF Repair (14), PDA closure (20), Blalock-Taussig shunt (5), CoA repair (8), Atrial septal defect repair (6), VSD with CoA/aortic arch repair (8)
		73 op	T13	4.5 months (1.4–18.6)	73 op	0	VSD (21), TOF (14), PDA (1), VSD+CoA/aortic arch hypoplasia (2), ASD (5), COA (5), Single ventricle (2), AVSD, complete (2) TOF + pulmonary atresia (4), UK (17)	VSD repair (13), PAB (7), PV/RVOT reconstruction (7) TOF Repair (10), PDA closure (1), Blalock-Taussig shunt (6) CoA repair (3), Atrial septal defect repair (6), VSD with CoA/aortic arch repair (1)
Kaneko et al., [31]	RCS	17	T18	mean, 129.52 days (range 7 to 402)	17	0	VSD + PDA(8), AVSD + CoA + PDA(1), VSD +CoA+ PDA (4), VSD+PDA+PAPVC(1), VSD (3)	ICR (3), P + SICR (4), P (10)
Kosiv et al., [32]	RCS	925	T18	NR	64	861	NR	NR
		555	T13	NR	37	518	NR	NR
Nakai et al., [33]	RCS	20	T18	35.4 ± 3.5 weeks	10	10	VSD + PDA (11), VSD + ASD + PDA (7), cAVSD + IAA + PDA (1), DORV and PDA (1)	
Graham et al., [34]	RCS	11	T13	77 days (4–2,375)	11	0	VSD (6) CoA (2) TOF (1) PDA (1), ASD (1), AVSD (1)	hemodynamic repair, PAB (9), systemic-to-pulmonary artery shunt (4), PDA ligation(1)
		24	T18	145 days (6–2,479)	24	0	VSD (14), CoA (2), TOF (5) PDA (2), ASD (1), AVSD (1)	
Peterson et al., [35]	RCS	8	T13	NR	2	6	VSD (11), ASD (8), PDA (8), Pulm valve stenosis (6), DORV (2), Aortic valve stenosis (2), Coarctation (3), TOF (1)	VSD closure+ ASD closure+ PDA ligation(2), PDA ligation(1), VSD closure+ ASD closure (1), VSD closure+ ASD closure+ PA band removal(1), VSD closure+ ASD closure+ pulmonary
		26	T18	NR	14	12		

								valvotomy(1), PA band+ PDA ligation
Swanson et al., [36]	RCS	56	T13/T18	92 days (40-144)	14	42	VSD (64%), AVSD (7%), TOF (14%), VSD +COA (14%)	
Kaneko et al., [37]	RCS	31	T13/T18	NR	4	27	VSD (1), VSD+ PDA(11), VSD+ MS(1), VSD+ PDA+ AS(1), DORV+ COA+ PDA(1), TOF+ PDA(1), DORV+ MA+ hypo LV+ IAA+ PDA+ AS(1), VSD+ MS+ PDA(1), DORV+ MA+ CoA(1), VSD+ PDA+ CoA(6), MS+ VSD+IAA+ Hypo LV(1), TA+ VSD(1), TOF (2), ToF+ PA(1), VSD+ASD+ PDA(1)	2 PAB, 2 PAB then CR
Weaver et al., [38]	RCS	10	T13/T18	mean 10.6 months (range from 2 to 32 months)	10	0	VSD (8); ASD (7); vulvar anomalies to include aortic, tricuspid, and pulmonary valve anomalies (4); aortic coarctation (2); DORV (2); and TOF (1)	ICR (10)
Domingo et al., [39]	RCS	49	T13	NR	49	0	NR	NR
		140	T18	NR	140	0	NR	NR
Kobayashi et al., [40]	RCS	5	T18	331.4 days	5	0	VSD+ PDAI(1), VSD+ PDA+ ASD+ LSVC(1), VSD+ CoA(1) VSD+ PDA+ASD(1), VSD+ CoA+ ASD(1)	4 PAB then CR, 1 CR
Maeda et al., [41]	Cohort study	27	T13	median 3 months (0 days–9.0 years)	6	21	VSD+ASD+PDA (1), ASD+PDA (1), AVSD+PDA(1), COA+VSD+PDA(1), IAA+APW+VSD (1), TOF (1)	PAB + DL (2), UK (1), ICR (2), BTS (1)
		134	T18	median 4.8 months (0 days–19.9 years)	32	102	VSD (13), VSD+PDA (8), VSD+PDA+ASD(2), VSD+PAPVC(2), COA+VSD (4), DORV+VSD+PS(1), DORV+VSD+MA+COA+AS (1), TOF (1)	PAB (11), ICR (3), UK (4), PAB + DL (7), ICR + PVR (1), PAB + COR (3), CS (1), BTS (1)

Notes: (a) Cooper et al., (30) had a study population of 304 and the number of surgical operations was 343. The number of operations is recorded above. More than the no of patients because so patients underwent more than one procedure, (b) The cardiac anomalies presented are those for the entire study population, not just for cardiac surgery. Except for Peterson et al., (35), where the cardiac anomalies are those for the intervention group only(c) Abbreviations, AC = atrioventricular canal, DORV: double outlet right ventricle; PAPV= partial anomalous pulmonary venous connection; COA =coarctation of aorta; AVSD=atrioventricular septal defects; VSD = ventricular septal defect; ASD = atrial septal defect; MA= mitral atresia; AS= aortic stenosis; PDA = patent ductus arteriosus; ICR=intracardiac repair; PAB=pulmonary arterial banding; SFA=subclavian flap aortoplasty; UK= unknown; CS= central shunt; BTS= Blalock-Taussig shunt; COR= coarctation of aorta repair; DL= ductus ligation; RCS=Retrospective Cohort Study; NC= Not Clear

3.4. Included studies

This systematic review includes 17 studies; 15 retrospective cohort studies, and 2 cohort studies. The retrospective studies sourced data by browsing through institutional databases for medical records. The 2 cohort studies sourced their data by conducting surveys, Bruns & Martinez, [27] from parents of children diagnosed with T13 or T18; and Maeda et al., [41] by sending questionnaires to different institutions about cases of T13 and T18 they had encountered. This paper reports a total of 2,551 trisomy cases. 672 cases were T13, 1478 cases were T18 and 401 cases were undefined since some studies did not separately report the two trisomies. Cardiac surgery was done on 814 patients (31.90% of the total study population), with 304 reported in Cooper et al., [30]. Of the 814 patients, 114 had T13, 368 had T18 and 332 were undefined.

3.5. Presentation of cases and intervention

Muneuchi et al., [24] had 34 T18 cases, 9 of them underwent cardiac surgery and 25 of them received conservative treatment. Costello et al., [26] had 3 T13 and 13 T18 patients. 7 T18 patients and 1 T13 patient received cardiac surgery as an intervention, while the rest of the cases underwent expectant treatment. In Bruns & Martinez, [27], a parent survey was used as the primary source for study data. There were 84 reported cases of trisomy 18, and only 24 of them received cardiac surgery. The type of intervention used for the other cases was not stated. Kwak et al., [28] had 11 cases of T18 and all underwent cardiac surgery. Rosenblum et al., [29] had 11 cases of T18 and 8 cases of T13; all underwent cardiac surgery. The study population in Cooper et al., [30] was 304 T18/ T13 patients. All of the patients underwent cardiac surgery, a total of 343 procedures; this is because some of the cases needed more than one procedure. Kaneko et al., [31] had 17 cases of T18, all of whom underwent heart surgery. In Kosiv et al., [32], only 63 out of 925 T18 patients and 37 out of 555 T13 patients received congenital heart surgery. The type of intervention accepted by the rest of the population is not clarified but it seems to be conservative treatment. Nakai et al., [33] had 20 T18 cases, 10 were treated surgically, and 10 were treated conservatively. In Graham et al., [34], all cases, 11 T13 and 24

T18 were treated using cardiac surgery. In Peterson et al., [35], 34 patients (8 T13 and 26 T18) were divided into three groups: complete, palliated, and non-intervention. In the study 16 patients, i.e. 2 T13 and 14 T18 patients (18 operations; complete repair in 11 and palliation in 7) received surgery and 18 patients did not. Swanson et al., [36] had a study population of 56. Unlike other studies, not all patients had a trisomy condition; 14 patients had T13 or T18 while 42 did not have any type of trisomy, but they all underwent cardiac surgery. A comparison was made for surgery outcomes in trisomy patients vs non-trisomy patients. Kaneko et al., [37] was done with 31 cases of T13 and T18 divided into three groups according to the medical treatment offered. In the first group (13 cases), both pharmacological ductal intervention and cardiac surgery were withheld. In the second group (9 cases), pharmacological ductal intervention was offered as an option, but cardiac surgery was withheld. Both strategies were available for the third group [9]. In the third group, where cardiac surgery was an option, only 4 of the patients underwent the procedure. Weaver et al., [38] had a population of 10 patients with T13 and T18 conditions. They all underwent surgical intervention. Domingo et al., [39] had 49 T13 and 140 T18 cases. All the patients underwent cardiac surgery. In Kobayashi et al., [40], there was 5 patients with T18, and all of them received the intervention. In Maeda et al., [41] 6 out of 27 cases of T13 and 32 out of 134 cases of T18 received cardiac surgery, with a considerable percentage of the surgery being palliative.

3.6. *Mortality and discharge rates*

The mortality outcome and discharge rate for all studies except are detailed in Table 3 below. The surgical intervention in Kwak et al., [28] was grouped into palliative surgery (n=3), total cardiac repair followed by palliative surgery (n=6), and one-stage total cardiac repair (n=2). The in-hospital mortality was 7/ 11. The survivors were 2 from one-stage total repair and two from complete repair followed by palliative surgery. No survivors were found after only palliative surgery. In Nakai et al., [33], the in-hospital mortality was 1/10(10%), and the overall mortality was 4/10(40%) in the surgical group. However, the authors report that the deaths were not due to cardiac-related issues. The in-hospital mortality in Peterson et al., [35] was 0/10 for the complete repair and 2/6 for the palliative surgery. The overall mortality was 2/10 for comprehensive repair, 5/6 for palliative surgery and 14/18 for the non-intervention group. Swanson et al., [36] reported that the in-hospital mortality was 1/14 (7%) in the surgical group and none in the control group. But it is prudent to note that the control group did not have any trisomy cases and hence no deaths.

Table 3: Mortality and Survival Outcome

	mortality					Trisomy	Discharge alive			
		Surgery intervention		Non-intervention			Surgery intervention		Non-intervention	
Study	mortality	Cases	Total N	Cases	Total N		Cases	Total N	Cases	Total N
Muneuchi et al., [24]	INH	2	9	20	25	T18	5	9	5	25
	OVR	4	9	21	25	T18	_	_	_	_
Costello et al., [26]	INH	0	1	2	2	T13	1	1	0	2
	INH	2	7	3	6	T18	5	7	3	6
	INH	2	8	5	8	T13/T18	6	8	3	8
Bruns & Martinez, [27]	OVR	3	24	17	60	T18	_	_	_	_
Kwak et al., [28]	INH	3	11			T18				
	OVR	7	11			T18				
Rosenblum et al., [29]	INH	0	8			T13	8	8		
	INH	0	11			T18	11	11		
	OVR (17.4 months)	5	19	37	45	T13/T18				
	OVR (17.4 months)	4	11			T18				
	OVR (17.4 months)	1	8			T13				
Cooper et al., [30]	INH	8	73			T13	65	73		
	INH	42	270			T18	228	270		
Kaneko et al., [31]	INH	3	17			T18	14	17		
	OVR	11	17			T18				
Kosiv et al., [32]	INH	11	37	284	518	T13	26	37	234	518
	INH	10	64	383	861	T18	54	64	478	861
Nakai et al., [33]	INH	1	10	8	10	T18	9	10	2	10
	INH	4	10	10	10	T18				
Graham et al., [34]	INH	0	11			T13	11	11		
	INH	3	35			T18	32	35		
Peterson et al., [35]	INH	2	16			T13/T18	14	16		
	OVR	5	16			T13/T18				
Swanson et al., [36]	INH	1	14	0	42	T13/T18	13	14	42	42
	OVR	3	11*			T13/T18				

Kaneko et al., [37]	INH	1	4	24	27	T13/T18	3	4	3	27
Domingo et al., [39]	INH	14	49			T13	35	49		
	INH	17	140			T18	123	140		
Kobayashi et al., [40]	INH	1	5			T18	4	5		
	OVR	3	5			T18				
Maeda et al., [41]	INH	14	32			T18	18	32		
	OVR	32	32			T18				
	OVR	3	6			T13				

(a)INH-In-hospital, OVR-overall (b) For Swanson et al., (36), 3 patients were lost to follow-up, thus the overall mortality was recorded out of [11].

When analyzing their data, some studies employed a Kaplan–Meier analysis to estimate the survival rates for longer time frames. Some other studies used Cox proportional hazard regression analysis to calculate the hazard/risk ratio that cardiac surgery and other risk factors had on the mortality of a trisomy patient. From performing a Kaplan–Meier analysis, Muneuchi et al., [24] found that the cumulative survival rates in the surgery group at 6 months, 12 months, and 24 months were 38%, 25%, and 22%, respectively, compared with 25%, 9%, and 9% in the conservative treatment group. The same analysis done by Rosenblum et al., [29], gave survival estimates in the surgical cohort, for one year and five years, as 79.9% and 66.6%, respectively. In the non-operative group, the survival estimate at one year was 34.2%, and the 5-year survival estimate was 24%. Cox proportional hazard regression analysis in Muneuchi et al., [24] revealed cardiac surgery as an independent hazardous variable for survival rate, with a hazard ratio of 5.53 (95% CI, 1.68 - 18.99), p = 0.006. Pre-operative assisted ventilation was also a hazardous variable with a hazard ratio of 2.27 (95% CI, 1.07- 5.24) p = 0.03. Analysis for survival time by Nakai et al., [33] found cardiac surgery to be a significant predictor, with a risk ratio of 0.12 (95% CI, 0.016– 0.63; p=0.01). Other reported variables were Apgar score at 5 minutes, and weaning from mechanical ventilation. Using the same analysis risk ratio for survival rate was found as 5.68 (95%CI, 2.00-16.09) in Rosenblum et al., [29]. Cooper et al., [30] associated prior cardiac surgery with better survival in T18 patients but not T13 patients, with an odds ratio of 0.2, p value<0.024 and in-hospital mortality by an odds ratio of 0.5, p value<0.068. Using Multiple Logistic Regression Analysis to examine the effect on mortality, Kosiv et al., [32] found that congenital heart surgery (CHS) had an odds ratio of 0.45 (95%CI, 0.21–0.97) for T13 and 0.43 (95%CI, 0.20–0.91) for T18. All the above Risk Ratio (RR) analyses are supported by findings from Kaneko et al., [37] and Kaneko et al., [31]. Kaneko et al., [31], using a log-rank test showed that surgery was significantly associated with longer postoperative survival (p = 0.02). Kaneko et al., [37], using univariate analysis, found being in group C (cardiac surgery) and having a higher Apgar score at 5 min were significantly related to more prolonged survival.

Table 4: Quality Appraisal

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Total score
Muneuchi et al., [24]	1	1	1	1	1	1	1	1	8
Costello et al., [26]	1	1	1	1	1	1	1	1	8
Bruns & Martinez, [27]	1	1	1	1	1	0	1	1	7
Kwak et al., [28]	1	0	1	1	0	1	1	1	6
Rosenblum et al., [29]	1	1	1	1	1	1	1	1	8
Cooper et al., [30]	1	0	1	1	0	1	1	1	6
Kaneko et al., [31]	1	0	1	1	0	1	1	1	6
Kosiv et al., [32]	1	1	1	1	1	1	1	1	8
Nakai et al., [33]	1	1	1	1	1	1	1	1	8
Graham et al., [34]	1	0	1	1	0	1	1	1	6
Peterson et al., [35]	1	1	1	1	1	1	1	1	8
Swanson et al., [36]	1	1	1	1	1	1	1	0	7
Kaneko et al., [37]	1	1	1	1	1	1	1	1	8
Weaver et al., [38]	1	0	1	1	0	1	1	1	6
Domingo et al., [39]	1	0	1	1	0	1	1	1	6
Kobayashi et al., [40]	1	0	1	1	0	1	1	1	6
Maeda et al., [41]	1	1	1	1	0	1	1	1	7

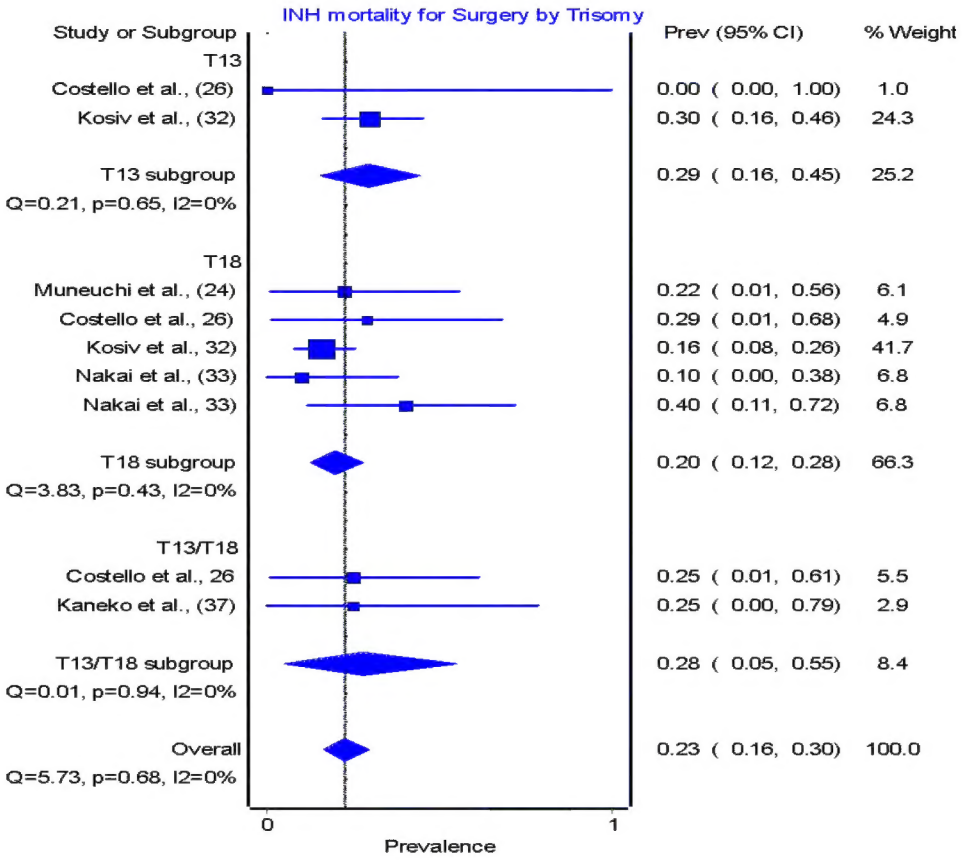

Fig 2: INH mortality for Surgery

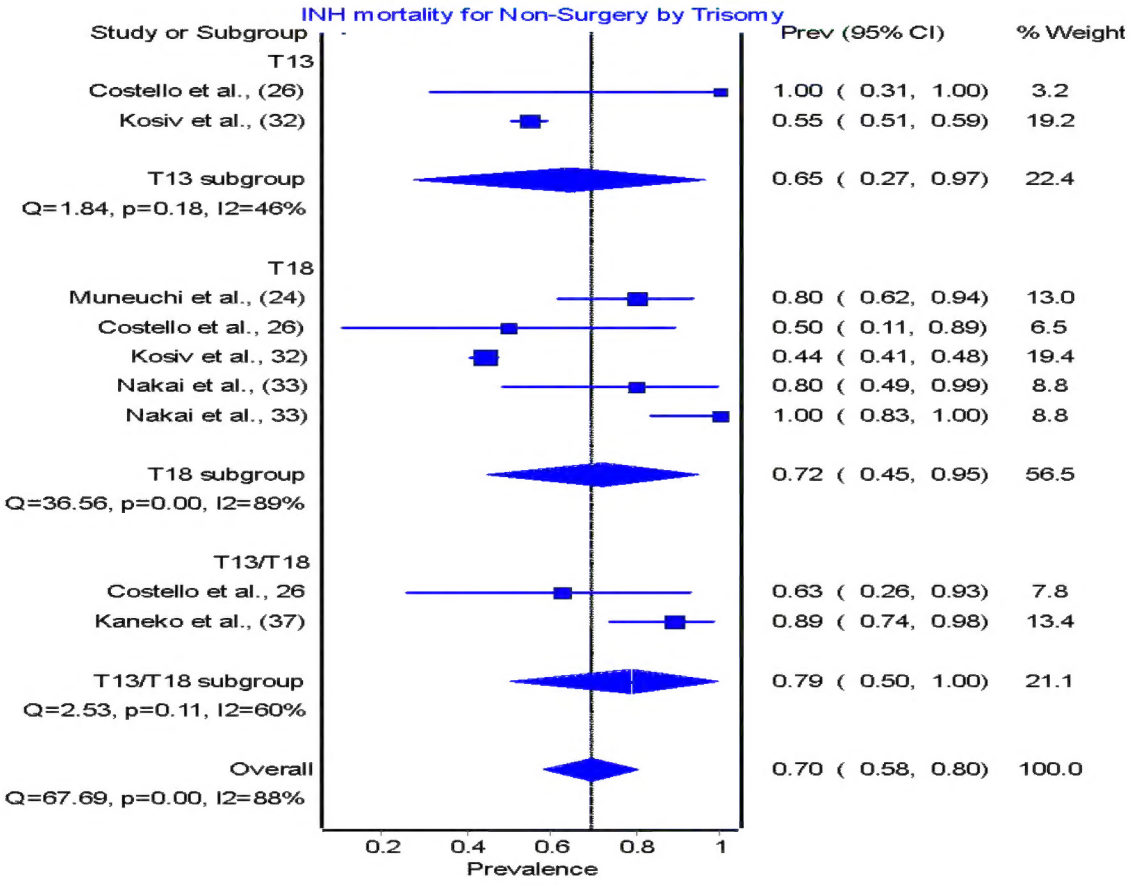

Fig 3: INH mortality for Non-surgery

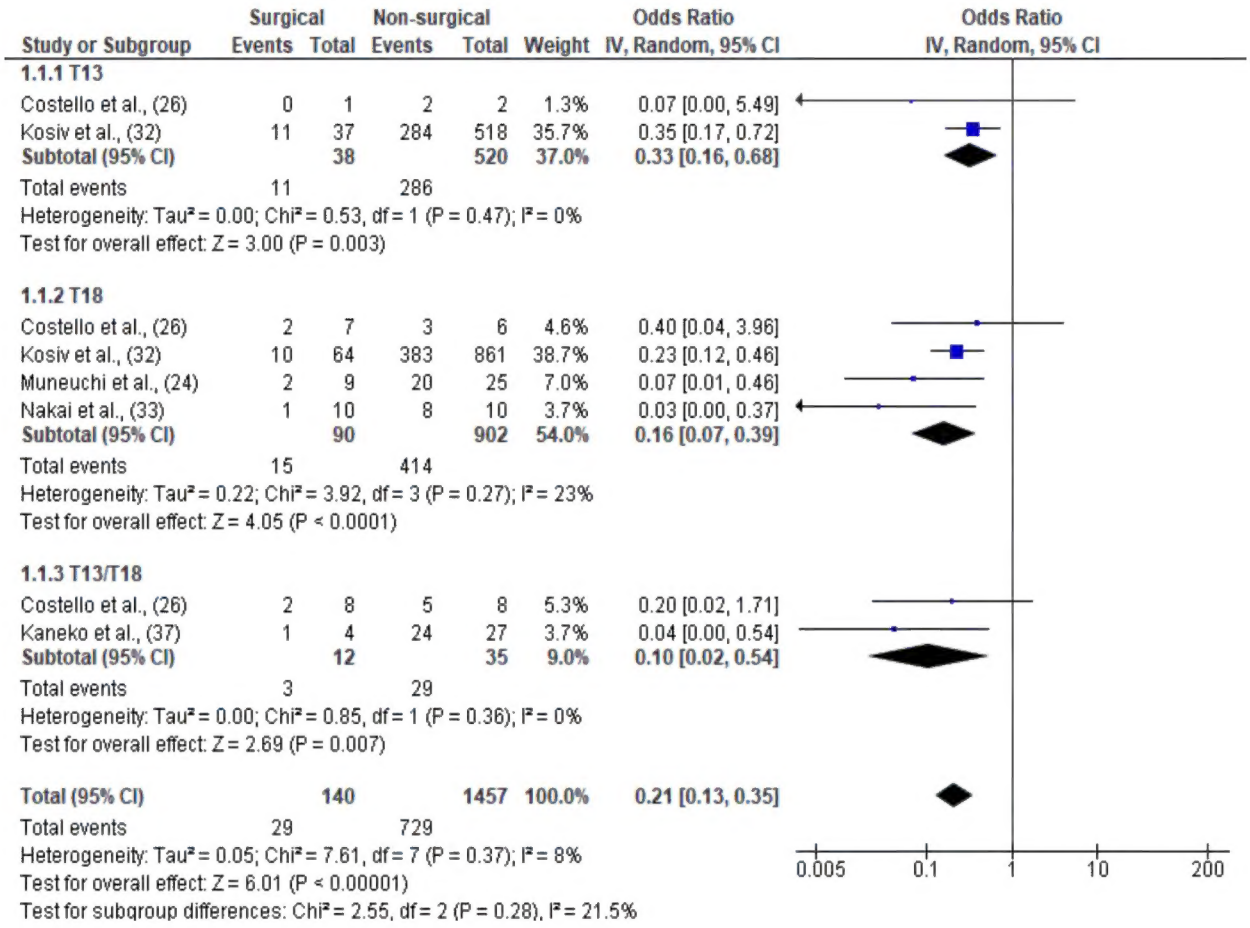
Surgical
Non-surgical
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 T13
Costello et al., (26) 0 1 2 2 1.3% 0.07 [0.00, 5.49]
Kosiv et al., (32) 11 37 284 518 35.7% 0.35 [0.17, 0.72]
Subtotal (95% CI) 38 520 37.0% 0.33 [0.16, 0.68]
Total events 11 286
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.00 (P = 0.003)
1.1.2 T18
Costello et al., (26) 2 7 3 6 4.6% 0.40 [0.04, 3.96]
Kosiv et al., (32) 10 64 383 861 38.7% 0.23 [0.12, 0.46]
Muneuchi et al., (24) 2 9 20 25 7.0% 0.07 [0.01, 0.46]
Nakai et al., (33) 1 10 8 10 3.7% 0.03 [0.00, 0.37]
Subtotal (95% CI) 90 902 54.0% 0.16 [0.07, 0.39]
Total events 15 414
Heterogeneity: Tau² = 0.22; Chi² = 3.92, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 4.05 (P < 0.0001)
1.1.3 T13/T18
Costello et al., (26) 2 8 5 8 5.3% 0.20 [0.02, 1.71]
Kaneko et al., (37) 1 4 24 27 3.7% 0.04 [0.00, 0.54]
Subtotal (95% CI) 12 35 9.0% 0.10 [0.02, 0.54]
Total events 3 29
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 2.69 (P = 0.007)
Total (95% CI) 140 1457 100.0% 0.21 [0.13, 0.35]
Total events 29 729
Heterogeneity: Tau² = 0.05; Chi² = 7.61, df = 7 (P = 0.37); I² = 8%
Test for overall effect: Z = 6.01 (P < 0.00001)
Test for subgroup differences: Chi² = 2.55, df = 2 (P = 0.28), I² = 21.5%
0.005
0.1
1
10
200

Fig 4: OR results for in-hospital mortality

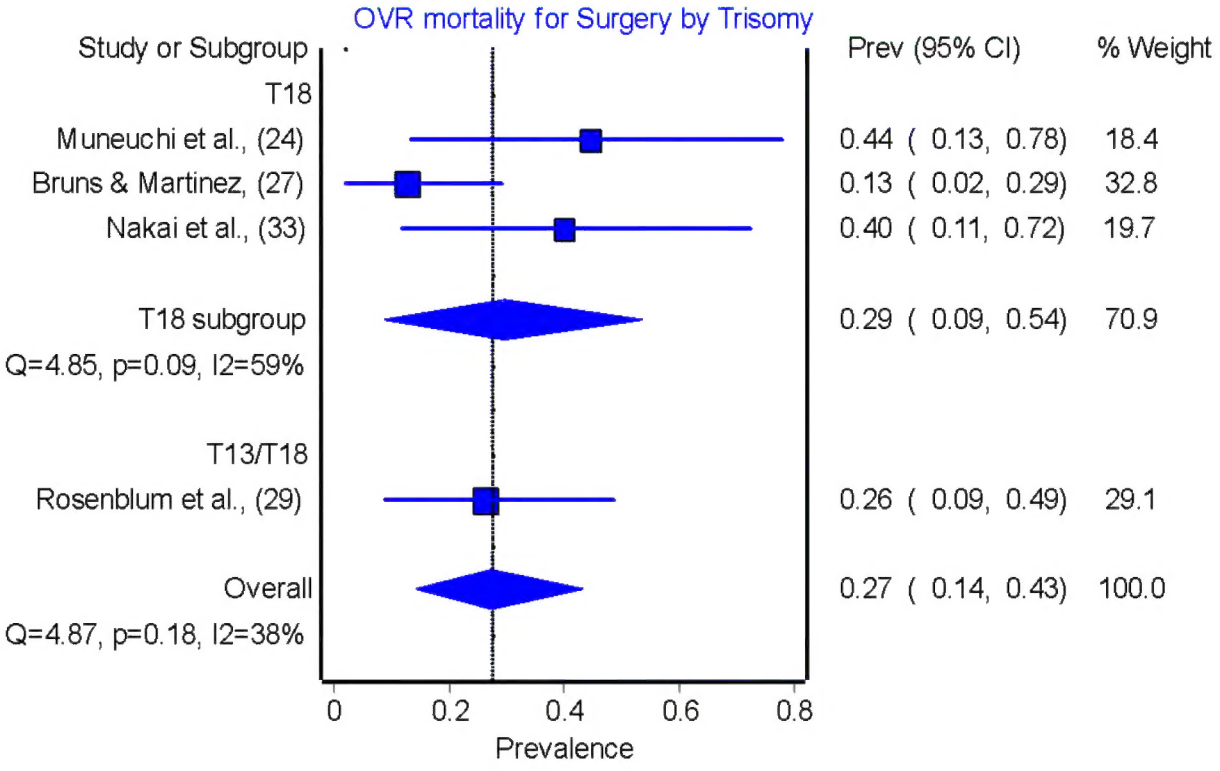

Fig 5: OVR mortality for surgery

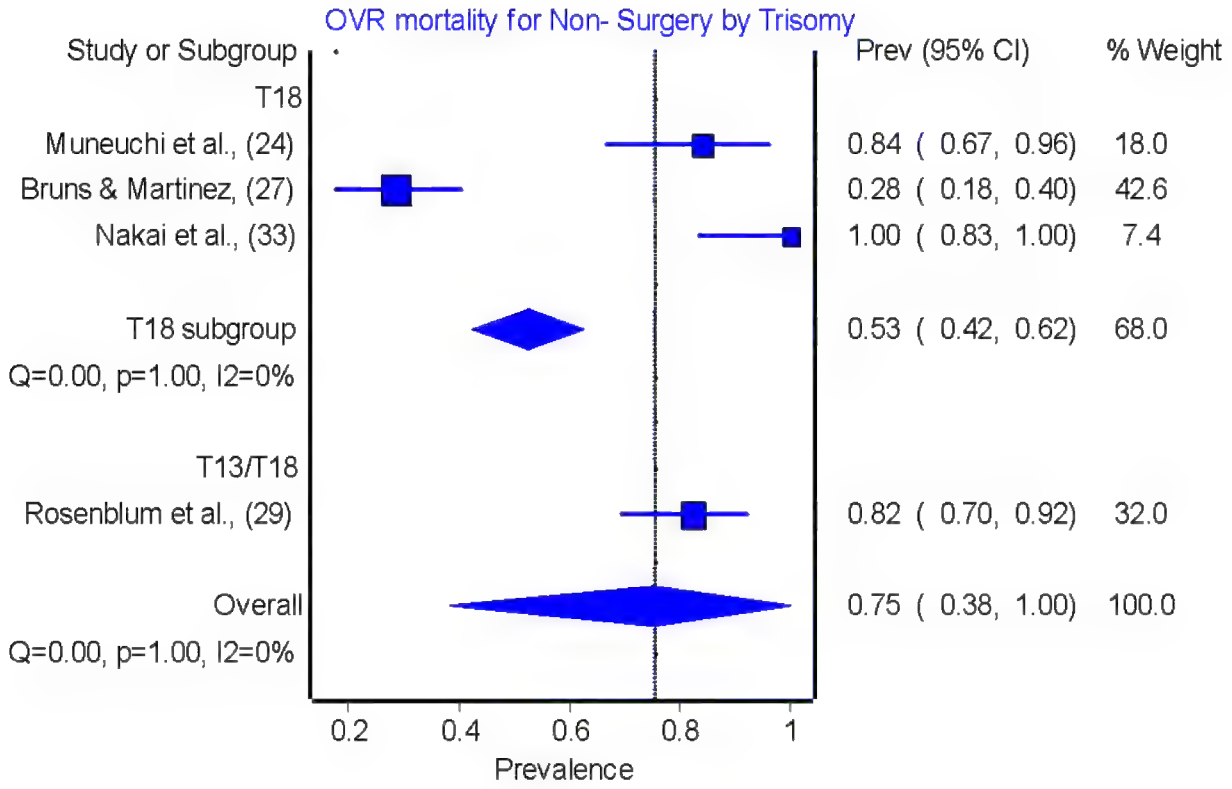

Fig 6: OVR mortality for Non-surgery

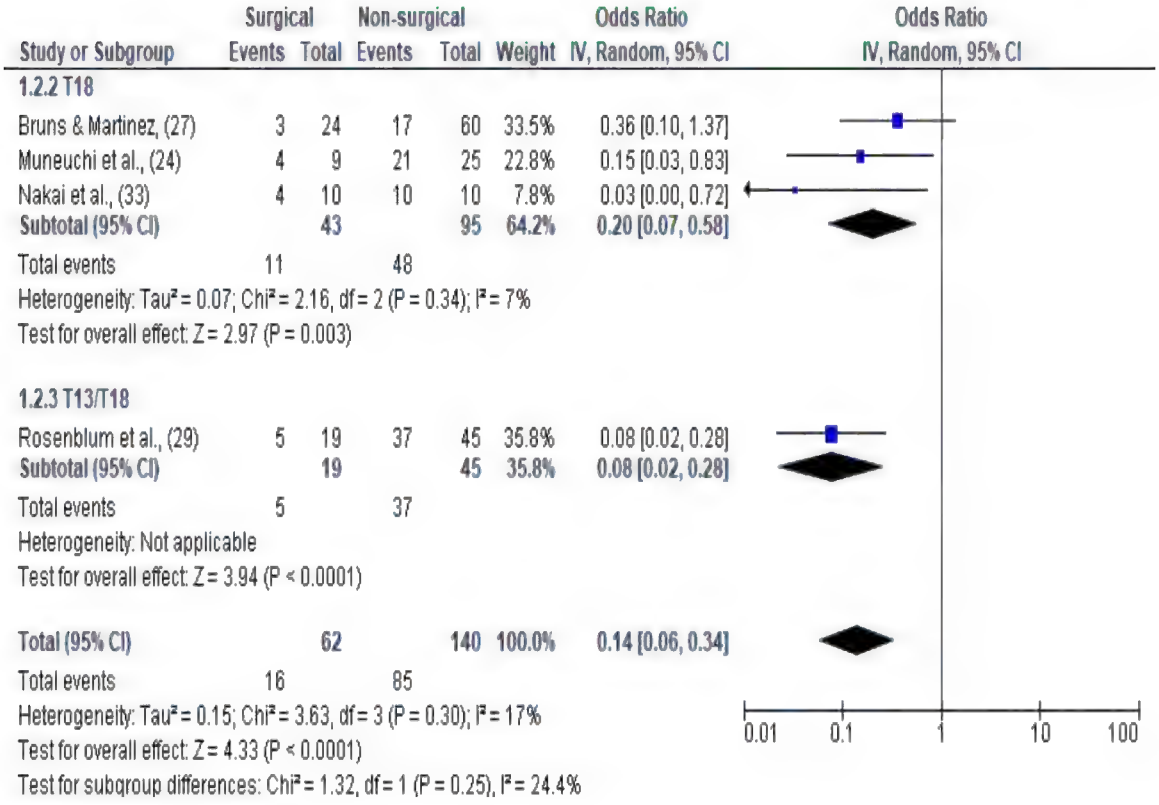
Surgical
Non-surgical
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.2.2 T18
Bruns & Martinez, (27) 3 24 17 60 33.5% 0.36 [0.10, 1.37]
Muneuchi et al., (24) 4 9 21 25 22.8% 0.15 [0.03, 0.83]
Nakai et al., (33) 4 10 10 10 7.8% 0.03 [0.00, 0.72]
Subtotal (95% CI) 43 95 64.2% 0.20 [0.07, 0.58]
Total events 11 48
Heterogeneity: Tau² = 0.07; Chi² = 2.16, df = 2 (P = 0.34); I² = 7%
Test for overall effect: Z = 2.97 (P = 0.003)
1.2.3 T13/T18
Rosenblum et al., (29) 5 19 37 45 35.8% 0.08 [0.02, 0.28]
Subtotal (95% CI) 19 45 35.8% 0.08 [0.02, 0.28]
Total events 5 37
Heterogeneity: Not applicable
Test for overall effect: Z = 3.94 (P < 0.0001)
Total (95% CI) 62 140 100.0% 0.14 [0.06, 0.34]
Total events 16 85
Heterogeneity: Tau² = 0.15; Chi² = 3.63, df = 3 (P = 0.30); I² = 17%
Test for overall effect: Z = 4.33 (P < 0.0001)
Test for subgroup differences: Chi² = 1.32, df = 1 (P = 0.25), I² = 24.4%
0.01
0.1
1
10
100

Fig 7: OR rates for OVR mortality

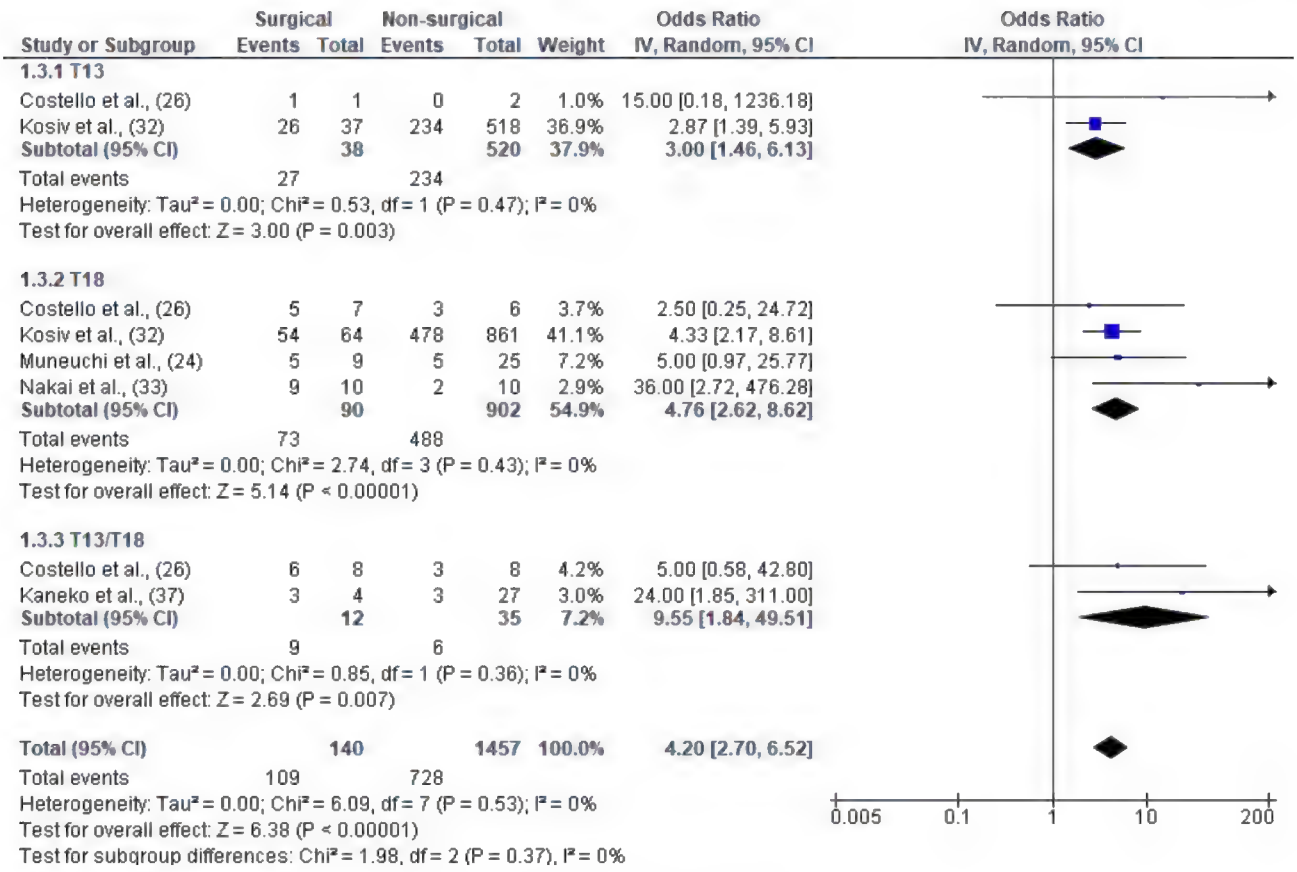
Surgical
Non-surgical
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.3.1 T13
Costello et al., (26) 1 1 0 2 1.0% 15.00 [0.18, 1236.18]
Kosiv et al., (32) 26 37 234 518 36.9% 2.87 [1.39, 5.93]
Subtotal (95% CI) 38 520 37.9% 3.00 [1.46, 6.13]
Total events 27 234
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.00 (P = 0.003)
1.3.2 T18
Costello et al., (26) 5 7 3 6 3.7% 2.50 [0.25, 24.72]
Kosiv et al., (32) 54 64 478 861 41.1% 4.33 [2.17, 8.61]
Muneuchi et al., (24) 5 9 5 25 7.2% 5.00 [0.97, 25.77]
Nakai et al., (33) 9 10 2 10 2.9% 36.00 [2.72, 476.28]
Subtotal (95% CI) 90 902 54.9% 4.76 [2.62, 8.62]
Total events 73 488
Heterogeneity: Tau² = 0.00; Chi² = 2.74, df = 3 (P = 0.43); I² = 0%
Test for overall effect: Z = 5.14 (P < 0.00001)
1.3.3 T13/T18
Costello et al., (26) 6 8 3 8 4.2% 5.00 [0.58, 42.80]
Kaneko et al., (37) 3 4 3 27 3.0% 24.00 [1.85, 311.00]
Subtotal (95% CI) 12 35 7.2% 9.55 [1.84, 49.51]
Total events 9 6
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 2.69 (P = 0.007)
Total (95% CI) 140 1457 100.0% 4.20 [2.70, 6.52]
Total events 109 728
Heterogeneity: Tau² = 0.00; Chi² = 6.09, df = 7 (P = 0.53); I² = 0%
Test for overall effect: Z = 6.38 (P < 0.00001)
Test for subgroup differences: Chi² = 1.98, df = 2 (P = 0.37), I² = 0%
0.005
0.1
1
10
200

Fig 8: OR results for Discharge rates

3.7. *Survival duration*

Some of the studies looked at the survival duration in the surgical groups and compared it to the no-intervention group, when possible. In Muneuchi et al., [24] the median survival duration in patients who underwent cardiac surgery was 22.4 (range, 3.3–241) months, compared to 0.9 (0–36.6) in the conservative treatment group. Kaneko et al., [31] had a postoperative survival time ranging from 0 to 1239 days (median, 179 days). The mean survival time for the surgical group in Nakai et al., [33] was 495.4 ± 512.6 days compared to 93.1 ± 76.2 days in the conservative group. Peterson et al., [35] presented the survival period among the three study groups. The median length of survival was 25.8 months (IQR 13.3–47), 2.6 months (IQR 1–3.5), and 0.15 months (IQR 0.05–3) for complete repair, palliated, and the non-intervention group, respectively. The median survival time for the surgical group in Swanson et al., [36] was 3.4 years (range, 2.1-10.5 years). This was the highest recorded time among the included studies.

3.8. *Postoperative complications*

To look at the safety of cardiac surgery in T13 and T18 patients, the occurrence of postoperative complications was considered. The prevalence and severity of complications varied across cases and studies, some were so severe that they led to recurrent surgery and even death caused by cardiac or cardiac-related complications. The complications were more prone in patients that received palliative/incomplete surgery instead of complete cardiac repair [28]. In Kwak et al., [28], there were 9 postoperative complications, five were from the group receiving palliative surgery only. Cardiac complications were arrhythmia without a pacemaker [1], pulmonary hypertensive crisis [1], and cardiac arrest [2]. Respiratory complications were chylothorax [1], pneumothorax [2], pleural effusion requiring drainage [4], pneumonia [2], Respiratory insufficiency requiring re-intubation [3], phrenic nerve injury/paralyzed diaphragm [4,28]. Acute Renal Failure requiring temporary dialysis occurred in 1 surgical procedure [28]. New onset seizures and sepsis infection occurred each twice in 2 separate surgeries [28]. For the surgical cohort in Rosenblum et al., [29], 15 patients (78.9%) did not show any major complications. For both T13 and T18 in Cooper et al., [30], the overall complication rate was 56% (n=192); 42 cases (57.5%) in T13 and 150 cases (55.6%) in the T18 group. Cardiac arrest in 23 (6.7%), arrhythmia requiring a pacemaker in 6 (1.7%), mechanical circulatory support in 7 (2.0%), and unplanned interventional cardiovascular procedure in 6 cases (1.7%)[30]. The most common complication was cardiac arrest in T13 cases (5 cases) and T18 cases (18 cases) [30]. In Kosiv et al., [32], infection complications occurred in 16 (43%) and 31 (48%) in the surgical group compared to 128 (25%) and 255 (30%) in the non-surgical group; for T13 and T18, respectively. In the T13/T18 cohort in Swanson et al., [36], 13/14 (93%) patients experienced at least 1 postoperative complication. In contrast, only 12 control patients (29%) had some type of postoperative complication.

3.9. *Functional Outcomes and Quality of life*

In only one study [38] out of 17 looked at the impact of cardiac surgery on functional outcomes and the quality of life in T13/T18 patients. The study objective for Weaver et al., [38] was to provide a summary of parental perspectives on quality of life, functional status, and hopes for T13/T18 children who had undergone heart surgery. The study data was from a survey done on parents of T13/T18 patients. When asked about the quality of life of T13/T18 patients, all parents selected "high". When asked to quantify the quality of life using a visual analogue scale (0 to 100), the mean response was 92.7 with a median of 90 (range, 80 to 100). The mean Functional Status

Scale (6 to 30, with 30 meaning worse functional outcome) was used to assess the functionality of the T13/T18 patients. The ranking by parents was 11 (range, 9 to 14) and that by pediatrician documentation, a day before discharge in the medical record, was 11.6 (range, 9 to 14).

3.10. Meta-Analysis

There are analysis results reported in some included studies, these are hazard/risk ratios (24) (29) (30) (31) (32) (33) (37). These analysis results are clearly presented but could not be applied for statistical analysis in this paper due to the use of two different methods (Cox proportional hazard regression analysis vs multiple Logistic Regression analysis) and different trisomy groups in studies (T13 vs T18 vs T13/T18). This review is of the opinion that performing meta-analysis using analyzed data barred with variability has the potential to produce meta-analysis with low-quality and incorrect results. The presentation of data in Table 3, showing the in-hospital mortality, overall mortality and discharge rates, made it possible to pool prevalence levels for the outcomes and to calculate the odds ratio of surgical intervention for in-hospital mortality, overall mortality and alive-discharge rate. The data could be divided into T13, T18 and T13/T18 in the sub-groups analysis. Only studies that had both surgical and control groups were included in the meta-analysis. One problem, however, is in the case of overall mortality. The quality of the analysis results of overall mortality will be in question due to differences in the length of the study period. The problem is that studies with longer follow-up timeframes will have higher overall mortality. The results for the overall mortality presented in this review should be taken at low accord. This problem may also seem to affect in-hospital mortality/ discharge rates due to varying lengths of hospital stay. However, the impact of surgical repair should be looked at from the perspective of its effect on the possibility of a patient improving in clinical condition and being discharged with improvement.

3.11. In-hospital mortality

The data for in-hospital mortality was from Muneuchi et al., [24], Costello et al., [26], Bruns & Martinez, [27], Kwak et al., [28], Rosenblum et al., [29], Cooper et al., [30], Kaneko et al., [31], Kosiv et al., [32], Nakai et al., [33], Graham et al., [34], Peterson et al., [35], and Kaneko et al., [37]. The pooled in-hospital mortality for the surgery group was 0.227 (95%CI, 0.164-0.296), p value=0.678 (Figure 2). In comparison, the pooled in-hospital mortality for the non-surgical group was 0.698 (95%CI, 0.581-0.803), p value=0.000 (Figure 3). A random-effects model was used in calculating the effect size. The Odds Ratio (OR) was 0.21 [95%CI, 0.13- 0.35], with a p-value <0.00001 (Figure 4). The results showed that the surgical intervention had a positive effect of reducing in-hospital mortality compared to non-surgery. The results were statistically significant. The in-hospital mortality for the surgical group was 29/140 compared to 729/1457 in the non-surgical group (Figure 4).

3.12. Overall mortality

Data used to calculate overall mortality was from Muneuchi et al., [24], Costello et al., [26], Bruns & Martinez, [27], Kwak et al., [28], Rosenblum et al., [29], Cooper et al., [30], Kaneko et al., [31], Kosiv et al., [32], and Nakai et al., [33]. The pooled overall mortality for the surgery group was 0.274(95%CI, 0.14-0.432), p value=0.181 (Figure 5). The pooled overall mortality for the non-surgical group was 0.754 (95%CI, 0.383-1.0), p value=1.000 (Figure 6). A random-effects model was used to calculate the association between surgical intervention and overall mortality. The Odds Ratio (OR) was 0.14 [95%CI, 0.06-0.34], with a p-value <0.0001 (Figure 7). The results showed that surgical intervention had a positive effect of reducing overall mortality compared to non-surgery. Furthermore, the results were statistically significant. The overall mortality, in this analysis, for the surgical group was 16/62 compared to 85/140 in the non-surgical group (Figure 7).

3.13. Discharge rate

The data for calculating the odds of discharge rate was from Muneuchi et al., [24], Costello et al., [26], Bruns & Martinez, [27], Kwak et al., [28], Rosenblum et al., [29], Cooper et al., [30], Kaneko et al., [31], Kosiv et al., [32], Nakai et al., [33], Graham et al., [34], and Peterson et al., [35]. A random-effects model was used in calculating the effect size. The estimated Odds Ratio (OR) was 4.20 [95%CI, 2.70- 6.52], with a p-value <0.00001 (Figure 8). The results showed that surgical intervention positively increased the discharge rate of trisomy patients compared to non-surgery. However, these results are not statistically significant. The discharge rate for the surgical group was 109/140 compared to 728/1457 in the non-surgical group (Figure 8).

4. DISCUSSION

Reports and outcome data from the included studies seem to agree that the use of surgical intervention for T13 and T18 patients positively reduces in-hospital and overall mortality. The survival rate pooled in this review (derived from overall mortality in Figures 5 and 6) was 72.6% in the surgery groups compared to 24.6% in the non-surgery groups. These survival rates are close to those presented in Muneuchi et al., [24] and Rosenblum et al., [29]. For example, the estimate for 5 years by Rosenblum et al., [29] is 66.6% in the surgical vs 24% in the non-surgical. They agree when comparing the calculated RR for discharge in this paper to the RR for survival reported in the studies. Muneuchi et al., [24] reported a RR of 5.53 (95% CI, 1.68 - 18.99), and Rosenblum et al., [29] an RR of 5.68 (95%CI, 2.00-16.09) for the impact of surgery on survival rate. These results are similar to those in this paper. The calculated Odds Ratio (OR) was 4.20 [95%CI, 2.70- 6.52], with a p-value <0.00001 (Figure 8). These results are also backed up by Kosiv et al., [32], Kaneko et al., [31], and Kaneko et al., [37]. Kosiv et al., [32] found that congenital heart surgery (CHS) had an odds ratio of 0.45 (95%CI, 0.21–0.97) for T13 and 0.43 (95%CI, 0.20–0.91) for T18 on mortality. Cooper et al., [30] reported an odds ratio of 0.5, p value<0.068 for in-hospital mortality in T13/T18. This meant that CHS had a negative effect on the mortality of T13 and T 18 patients. The T13 vs T18 in-hospital mortality for the surgical groups was 0.29 (95%CI, 0.16-0.46) vs 0.20 (95%CI, 0.12-0.28) (Figure 2). From the p-value, these results are statistically insignificant, however, they do show that cardiac surgery had more impact on T18 patients than on T13 patients. This seems to be the case when Odds ratios are looked at. The calculated ORs for T13 vs T18 in terms of in-hospital mortality are 0.33 (95%CI, 0.16-0.68) vs 0.16 (95%CI, 0.07-0.39) (Figure 4). The calculated OR for discharge rates in T13 vs T18 patients are 3.00 (95%CI, 1.46-6.13) vs 4.76 (95%CI, 2.62-8.62) (Figure 8). Also, the study Cooper et al., [30], using an odds ratio, associated prior cardiac surgery with better survival, in T18 patients but not T13 patients. The explanation for this may be that cardiac surgery produces a

better outcome in T18 patients than in T13 patients. Another reason could be that the overall severity of T18 cases presented in this review was lower than T13 cases. The second point, however, may be proven null when the in-hospital mortality rates for T13 vs T18 patients in the non-surgical groups are looked at. The prevalence rates for in-hospital deaths in the non-surgical T13 vs T18 groups was 0.65 (95%CI, 0.27-0.97) vs. 0.72 (95%CI, 0.45-0.95). The death rate for those who did not receive surgery was approximately 7% higher in the T18 group, showing that the severity of T18 cases was neither low nor mild. The above data support the use of cardiac surgery in the management of trisomy 13 and trisomy 18 patients. It is, however, good to also consider the occurrence of complications and the functional outcomes arising from this intervention. Generally, there was a low number of reported complications. The lowest number of complications was recorded by Kwak et al., [28]; there were 9 postoperative complications. Rosenblum et al., [29] reported a complication rate of 21.1%. The highest number was recorded by Swanson et al., [36], where 93% of the patients had at least 1 postoperative complication.It is prudent to note that patients suffering from T13 and T18, full or mosaic, did experience complications, whether they underwent surgery or not. In Kosiv et al., [32], infection complications occurred in 16 (43%) and 31 (48%) in the surgical group compared to 128 (25%) and 255 (30%) in the non-surgical group; for T13 and T18, respectively.

4.1. Study Limitations

The variability in which data was analyzed and presented created a challenge when synthesizing data. The reason for variability may be because the included studies were all cohort studies based on past medical records (and one survey), which may have been archived and stored differently.

4.2. Implication on study

To the best of the gathered research, no systematic review has been published discussing the impact of cardiac surgery on the mortality outcome in patients with T13 or T18. This systematic review and meta-analysis paper fills that research gap.

5. CONCLUSIONS

In conclusion, the use of cardiac surgery for trisomy patients positively reduces in-hospital mortality compared to non-surgery OR= 0.21 [95%CI, 0.13- 0.35], with a p-value <0.00001. A pooled prevalence supports this for in-hospital deaths of 0.227 (95%CI, 0.164-0.296) in the surgical group compared to 0.698 (95%CI, 0.581-0.803) in the non-surgical group. Cardiac surgery also seems to have a positive impact on reducing overall mortality. The study results showed that the use of cardiac surgery positively impacted mortality, but there were also reported cases of postoperative complications. Therefore, this intervention seems plausible but the physician should consider the possibility of complications.

5.1. Recommendations

All of the data used in this review are from observational studies (retrospective cohort studies). However, more studies on the effect of cardiac surgery – especially those examining T13 and T18 separately – should be done.

6. AUTHORS CONTRIBUTION STATEMENT

Dr. Samer A. Alzahrani has designed and done the review study, Dr. Mohannad A. Alghamdi (corresponding author) wrote the entire manuscript and edited the manuscript; Mohammed F. Bin Muammar, Dr. Abdulhakeem Mahmoud A Khan and Dr.Raghda Khaled Tayeb were also helped in designing the study and reviewed the manuscript. All authors equally contributed to the manuscript

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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